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The Impact of Intravenous Tranexamic Acid on Hemoglobin and Hematocrit Levels after Cesarean Delivery in Women at Low Risk for Postpartum Hemorrhage: A Randomized Controlled Trial

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ABSTRACT

Background & aim: Cesarean section (CS) results in about twice the blood loss as vaginal delivery. Blood loss can cause decreased hemoglobin and hematocrit. Few studies have been done on the effect of tranexamic acid on hemoglobin and hematocrit levels after delivery with controversial results. This study was therefore designed to determine the effect of intravenous tranexamic acid on hemoglobin and hematocrit after CS in women at low risk for postpartum hemorrhage.

Methods: This randomized controlled trial was performed on 50 pregnant women referred to Izadi hospital, Qom, Iran, from August 15, 2016 to April 30, 2017. Subjects were randomly assigned into two groups of 25 using block randomization. The intervention group received 1 gr tranexamic acid 10 minutes before CS, while the control group received 1 gr distilled water. Hemoglobin and hematocrit were measured before and 12-24 hours after delivery. Also, the volume of blood loss from placental delivery was measured 2 hours after delivery. T-test was used to compare the differences between the two groups.

Results: There was no significant difference in pre-operative and 12-24 h post-operative hemoglobin (12.17±1.21 vs 11.72±0.99 mg/dl) and hematocrit (37.73±2.38 vs 36.22±2.41mg/dl) in the two groups (P>0.05). However, Tranexamic acid significantly reduced the volume of total blood loss from placental delivery in the first 2 hours after delivery (616.32±176.87 vs 731.45±178.79mg/dl, P=0.028).

Conclusion: Reduced blood loss after tranexamic acid was not associated with improvement of post-operative hemoglobin and hematocrit. Therefore, tranexamic acid should be prescribed according to the clinical condition and possible complications.

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Introduction

Postpartum hemorrhage (PPH) is the third-most common cause of maternal death in the United States and is still the first prevalent cause of maternal death in developing countries (1). PPH is classically defined as blood loss of more than 500 ml following vaginal delivery or more than 1000 ml following caesarean section (CS) (2). According to the World Health Organization (WHO), the rate of caesarean section continues to rise globally, now accounting for more than 1 in 5 (21%) of all childbirths. This rate is set to continue increasing over the coming decade, with nearly a third (29%) of all births likely will be performed through caesarean section by

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2030 (3). Hemorrhage and anemia are serious complications of cesarean delivery. In order to decrease maternal morbidity and mortality caused by bleeding and hemoglobin drop, it is vital to reduce severe bleeding and anemia (4).

Antifibrinolytic agents, mainly tranexamic acid (TA), have been demonstrated to reduce blood loss and transfusion requirements in various surgical procedures, such as coronary artery bypass, scoliosis surgery and knee arthroplasty (4-11). Many randomized controlled trials and meta-analyses in the field of obstetrics have suggested that TA administration in women after vaginal or elective caesarean delivery reduces blood loss and the incidence of PPH (6, 12-22). But few studies have been done on the effect of tranexamic acid on hemoglobin and hematocrit levels after delivery. Some clinical trial studies have reported controversial results in this regard (6, 19, 23, 24). Therefore, this study was conducted to evaluate the effect of tranexamic acid on hemoglobin and hematocrit levels after cesarean delivery.

Materials and Methods

This randomized controlled trial (RCT) was conducted on 50 women undergoing cesarean section at Izadi Hospital, Qom, Iran, from August 15, 2016, to April 30, 2017. The study was approved by the ethics committee of Qom University of Medical Sciences (code No: MUQ.REC.1394.154). It was prospectively registered in the Iranian Registry of Clinical Trials (code No: IRCT20091010002558N7.). Oral and written informed consent was obtained from all participants.

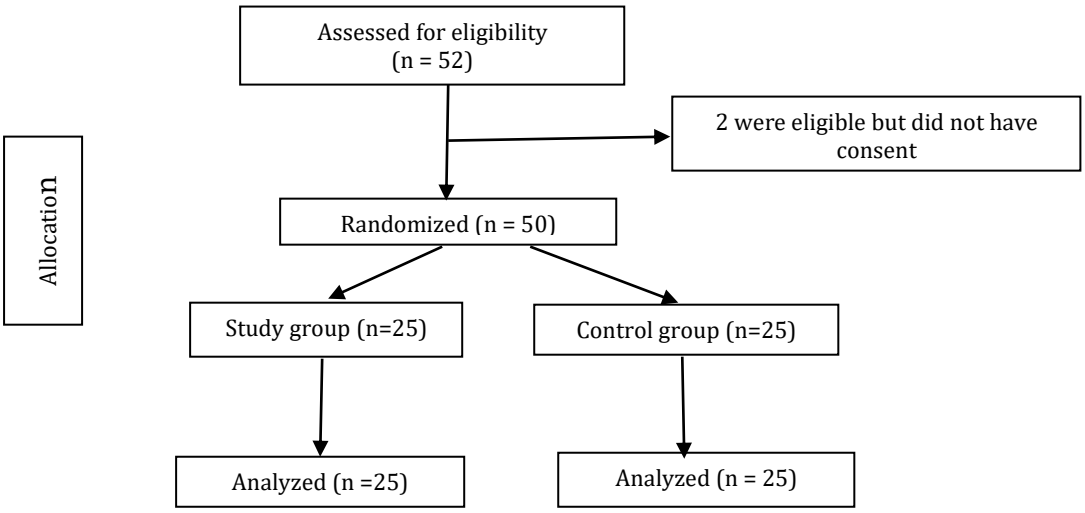
Pregnant women who wanted to undergo elective cesarean delivery by Pfannenstiel incision under spinal anesthesia were eligible for the study. Inclusion criteria were women aged 18–35 years with a singleton pregnancy at 38-42 weeks of gestation and blood pressure < 140/90 mmHg.

The women with pre-eclampsia, polyhydramnios, macrosomia, preterm labour, multiple pregnancies, placenta praevia, abruptio placenta, abnormal placenta, thrombophilia, anemia, coagulopathy, cardiovascular, renal, liver disorders and allergy to tranexamic acid were excluded from the study.

Considering that in the study of Movafegh (6), the mean of hemoglobin decline was 1±0.4 in the study group and 1.8±0.7 in the control group, regarding to 80 % power and 5 % probability of type 1 error, the sample size was calculated as 22 subjects in each group. Adjusting for drop out, recruitment target was set at 25 subjects per group. Figure 1 showed the summary of study's design.

$$n = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2(\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)^2}$$

Figure1. CONSORT Flowchart



The women were randomly allocated into two groups of study and control based on the block randomization. Block size 4 was considered. So we have six quadruple blocks consisting of AABB, ABAB, BBAA, BABA, ABBA, BAAB. The selection of each block will also be random and will be done using dice. For example, if the number 3 is rolled in a dice, the BBAA block is considered, so the first two patients are assigned to treatment B and the next two patients to treatment A. The dice will be thrown ten times to complete the patients' assignment to treatment groups. Assignment of treatment to groups A and B will also be based on accident (coin toss).

Women in the study group (n=25) received 1 gr intravenous TA, 10 min before skin incision, and the control group (n=25) received 1 gr distilled water as placebo in 200 mL normal saline over 10 min. Two women were excluded from the study because they didn't have consent to participate in the study. TA was supplied in 2 × 500 mg/5 mL ampoules (made by kharazmi Pharmaceutical Company, Iran). The placebo comprised 2×5 ml distilled water ampoules (made by Shahid Ghazi Pharmaceutical Company, Tabriz, Iran).

To hide the medication allocation, two vials of the tranexamic acid and distilled water were placed in similar opaque sequentially numbered sealed packages by an operator room technician that not involved in sampling and analysis, who maintained the medication administration code. In this way, the data evaluators and participants were not aware about the study medication.

Haemoglobin and haematocrit levels were measured before and 12–24 h after cesarean delivery. Blood loss was measured from placenta delivery to two hours after cesarean section (blood and amniotic fluid before placenta delivery was not collected or measured). Blood-soaked gauzes, gowns, sheets and tampons were all weighted before and after use, and blood loss was estimated using the method adopted by Gai et al., as follows (5):

The volume of blood (mL) = (weight of used materials _ weight of materials prior to use)/1.05 and then plus the volume included in the suction container after placental delivery.

Immediately after cesarean delivery, a sterile disposable plastic cover with known weight was placed under the mother to collect blood loss and then was weighted. An electronic scale (with a 1-g deviation range) was used for measuring the weight of gauzes, gowns, sheets and pads. All operation was done by the researcher. Collection of data was performed by one physician.

Both groups received 20 IU oxytocin in 1000 mL of normal saline over 20 min after placental delivery. The dose of received oxytocin and other additional uterotonic were recorded for both groups.

Vital signs (heart rate, blood pressure and respiratory rate) were recorded before, 1 and 2 hours after cesarean delivery. Complete blood count (CBC) was performed 12-24 h after delivery. Creatinine, BUN and urine analysis were performed before delivery, and 48-72 hours after delivery.

Data were analyzed by SPSS software (version 17) (IBM SPSS, New York, NY, USA). T-test was used to compare the differences between the two groups described with 95 % confidence intervals (95 % CI). $P< 0.05$ was considered statistically significant.

Results

The women's characteristics were similar in the two groups, with no statistical difference between the two groups (Table 1).

No significant difference was found between the two groups in terms of pre-operative hemoglobin and hematocrit (12.17±1.21 vs 13.35± 1.37). The hemoglobin and hematocrit levels decreased slightly after CS in the two groups, but there was no statistical difference($p=0.43$).

The mean of hemoglobin and hematocrit drop before and after the intervention was not significantly different between the two groups (Hb: 0.458±0.75 vs 0.945±1.25 and Hct: 1.508±2.41 vs 0.395±3.34) (Table2). Total blood loss from placental delivery to 2 h postpartum reduced in the study group, the two groups were significantly different in this regard ($P = 0.028$) (Table2).

Table1. The characteristics of women in the study and control groups

Characteristics	Study Mean±SD	Control Mean±SD	p-value
Age	30.48±4.71	31.46±4.85	0.973
Height	159.76±5042	160.18±7.33	0.894
Weight	64.92±14.45	67.71±14.18	0.906
BMI	25.31±4.94	26.43±4.75	0.930
Weight gain	10.52±4.03	12.72±4.07	0.852
Gravida	2.32±0.74	2.29±0.80	0.739
Parity	1.16±0.55	1.13±0.61	0.818
Gestational age	38.24±0.436	37.83±1.76	0.274
Number of CS	1.21±0.50	1.04±0.62	0.563

There was total reduction in blood loss by about 18.7 % in the study group.

There was no significant difference between the two groups in the BUN, Cr and urine analysis before and48-72h after CS (p=0.48).

There was no significant difference between the two groups in the vital signs (heart rates, respiratory rates and blood pressures) before and 1-2 hours after CS (p=0.12).

There was no significant difference between the two groups in the 1 and 5 minutes Apgar scores (p=0.62).

No side effects of tranexamic acid such as nausea, vomiting and diarrhea were reported in the study group.

Table 2. The main outcomes in the two groups

Variables	Study group (Mean±SD)	Control group (Mean±SD)	P value
Pre-operative Hb* level (mg/dl)	12.17±1.21	13.35±1.37	0.456
12-24 h post-operative Hb level (mg/dl)	11.72±0.99	11.41±1.6	0.43
Mean Hb drop before and after intervention	0.458±0.75	0.945±1.25	0.11
Pre-operative Hct** level(%)	37.73±2.38	37.70±3.45	0.17
12-24h post-operative Hct level (%)	36.22±2.41	37.31±3.04	0.15
Mean Hct drop before and after intervention	1.508±2.41	0.395±3.34	0.42
Total blood loss from placental delivery to 2 h postpartum(ml)	616.32±176.87	731.45±178.79	0.028

*Hb: hemoglobin **Hct: hematocrit

There were no episodes of thrombosis in the study group 24h after delivery.

No PPH was reported and no blood transfusion was needed in the two groups.

Additionally, there was no statistical difference between the two groups in the additional uterotonic drugs (P=0.75).

Discussion

In this study, the effect of tranexamic acid on hemoglobin and hematocrit levels after cesarean delivery was investigated. The findings of the present study demonstrated that administration of 1 gr intravenous tranexamic acid 10 min before skin incision didn't cause a significant difference between the two groups in 12-24 h post-operative hemoglobin and hematocrit levels. There was total reduction in blood loss by about 18.7% in the study group. According to some studies, reduction in total blood loss in the study group was about 17% and 18% (5,12).

There are few studies on the effect of tranexamic acid on hemoglobin and hematocrit levels after delivery.

A similar study by Mirghafoorvand et al. (23) entitled as "The Effect of Intravenous Tranexamic Acid on Hemoglobin and Hematocrit Levels after Vaginal Delivery" Reported that the mean of hemoglobin level before and after the intervention was not significantly different between the two groups . But the mean of hematocrit loss was lower in

the intervention group than control group (p=0.03).

In the study by Loic Sentilhes et al. (4), in addition to prophylactic oxytocin, 1 gr of tranexamic acid or placebo was administered intravenously after delivery. They showed that among women with vaginal delivery who received prophylactic oxytocin, the use of tranexamic acid did not result in a rate of postpartum hemorrhage of at least 500 ml that was significantly lower than the rate with placebo. Also, there was no statistically significant difference between the two groups in peripartum change in haemoglobin and haematocrit levels. These results were consistent with the results of the present study.

In the study of Movafegh et al. (6), 10 mg/kg tranexamic acid was administered 20 minutes before skin incision at cesarean delivery. Blood loss was significantly lower in the TA group than in the control group. Also, there was no significant difference between the study group and control group in pre-operative and 24 hours post-operative haemoglobin levels. These results were similar to the findings of the present study.

Irene ray et al. (19) in their study administered 1 gr IV tranexamic acid 20 min before skin incision at caesarean delivery and found that the mean intra-operative and post-partum blood loss was significantly lower in the study group than the control group. The difference between the pre-operative and post-operative hemoglobin levels was significantly lower in the study group than the control group. The decrease in hemoglobin level in the study group could be due to the fact that, the mean of pre-operation hemoglobin was 10.33±1.26 mg/dl in the study group and 9.80±1.34 mg/dl in the control group (p=0.05). This may be due to the fact that the hemoglobin level in the control group was lower from the beginning of the study.

The study of Amr yehia et al. (24) aimed to evaluate the efficacy of tranexamic acid in reduction of blood loss during and after cesarean section. Twenty-four hours' post-operative hemoglobin and hematocrit levels were significantly higher in the study group compared to controls. These results may be due to the fact that they injected tranexamic acid after delivery of the baby. We hypothesized that this may be due to the time of tranexamic acid administration.

According to the results of the present study, there were no abnormalities in CBC, urinalysis, renal function tests before or after tranexamic acid administration. These results were comparable with some other studies (5,6,19).

Also, in the present study, no significant abnormal vital signs occurred after TA administration. This has been confirmed by other studies (5,6,15,19).

According to the present study, the side effects of intravenous tranexamic acid such as nausea, vomiting and diarrhea were similar in the two groups. These results were similar to the findings of previous studies (19).

No PPH was reported in the present study. The patients with blood loss more than 1000 ml were defined as PPH in our study. While, PPH has been defined as blood loss more than 400 ml in the studies of Gai et al. (5) and Yang et al. (25) and more than 500 ml in the study of Jianjun Xu et al. (15).

Additionally, administration of oxytocin and other uterotonic drugs were not statistically different in the two groups. While, in the study of Movafegh et al., oxytocin administration was significantly less in the study group compared to the control group (6).

The incidence of thrombosis during pregnancy and puerperium is 5–6 times higher than that in the general population. When the antifibrinolytic drug tranexamic acid is administered, the increased risk of thrombosis should be considered, especially in the CS post-partum women (5,18). In the current study, no signs of thrombosis were found in the mothers. Similar results were reported in other studies (5,6,8,15,19).

The results in the present study demonstrated that TA can be used safely without increasing the occurrence of thrombosis, but still more researches are needed in this regard.

The safety of giving TA (1 g) while the fetus is still in utero was an important concern. As a consequence, the neonatal outcome was accurately evaluated by a neonatologist. In the current study, there was no significant difference between the two groups in 1 and 5

minutes Apgar scores. None of the neonates required NICU admission. These results were comparable to the previous studies (5,19).

The strength of the study is that the necessary blinding was performed in the clinical trial.

The limitations of the present study include: only English or Persian articles were obtained, the study was not powered to test all side effects of the drug. More study should be implemented to investigate the safety of TA in future studies.

The practical results of the present study showed that TA administration reduces the volume of bleeding in the first 2 hours after delivery, but this reduction was not effective on hemoglobin and hematocrit levels. Therefore, it should be prescribed according to the clinical condition and possible complications.

Conclusion

Reduced blood loss after tranexamic acid was not associated with improvement of post-operative hemoglobin and hematocrit levels. While TA administration reduces the volume of bleeding in the first 2 hours after delivery in the study group.

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Conflicts of interest

Authors declared no conflicts of interest.

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